in the specification on page 5. The Johnson et al. patent discloses the administration of an LRF analog substituted in the 6-position by either D-Trp, D-Phe or D-Tyr and having the ethylamide modification instead of glycine in the 10-position. The Peptides 1976 article, co-authored by the Applicants, discloses the synthesis and testing of a number of similar analogs wherein D-Ala, D-Leu or D-Lys is substituted in the 6-position. The '726 patent to Schally et al. discloses [D-Phe^6]-LRF and the '125 patent to Schally et al. discloses [D-Trp^6]-LRF.

U.S. Patent No. 4,086,219 to Wittle et al., to which the Examiner directs specific attention, is directed to an allegedly new and more potent nonapeptide which is an LRF analog wherein the amino acid residue at the 1-position has been deleted. More particularly, Wittle et al. assert that such nonapeptides are LRF-antagonists -- not agonists, as the peptides of the invention are characterized. However, it is submitted that the disclosure of Wittle et al. is arguably less pertinent than that of the other references, such as the Peptides 1976 article, and is certainly no more pertinent. Aside and apart from the teaching of Wittle et al. with respect to the deletion of the amino acid residue in the 1-position, they disclose no more than what is admitted in the specification, that it has been known to make D-isomer substitutions in the 6-position of LRF analogs. In this respect, Wittle et al. simply list some sixteen possible D-isomers of amino acids and say that they can be substituted in the 6-position of their particular nonapeptide. It is pointed out at page 4, lines 23 et seq. of the specification

that the substitution of D-amino acids for glycine in the 6-position of LRF analogs is known.

Certainly, Wittle et al. does not constitute any particular teaching that the D-isomer of histidine in the 6-position has any particular potency that would make it stand out from the rest of the group of sixteen with which it is included. Viewed objectively, Wittle et al. give examples of the synthesis of eight different LRF analogs each having a D-isomer substitution in the 6-position, with the substitutions being as follows:

EXAMPLE:

1. D-Phe
2. D-Trp
3. D-Trp
4. D-Trp
5. D-Leu
6. D-Asp
7. D-Phe
8. D-Trp

Moreover, Wittle et al. specifically claim nine LRF analogs including the foregoing eight synthesized in the Examples and one wherein D-Ser is present. Thus, Wittle et al. (other than providing a listing of sixteen potential D-isomer amino acids for substitution in the 6-position) do not disclose more than Applicants admit, namely, that D-isomer substitutions in the 6-position are known. If anything, viewed objectively, one would tend to ignore the presence of D-His among the sixteen potential substituents because it is neither present in one of the analogs synthesized in the Examples or in one of the analogs claimed, and in this respect Wittle et al. actually would lead one away from this particular substitution. However, more importantly, Wittle

et al. are concerned with the synthesis of an LRF analog having antagonistic properties rather than one which is an agonist.

In addition to the foregoing, it is emphasized that no reference teaches the substitution of imidazole benzyl D-His in the 6-position of an LRF analog.

In the last sentence of the Office Action, the Examiner made reference to the comparison of the peptides of the invention with other known analogs of LRF and an Affidavit has been prepared for signature by Dr. Wylie W. Vale, Jr., which will be filed before the end of this month. The Affidavit points out the substantially improved hydrophilicity and biological potency of the peptides of the invention, and it is believed that it provides convincing proof of the nonobviousness of the peptides of the invention.

In view of the foregoing, it is believed that the application presents claims to subject matter clearly patentable over the prior art and favorable action is courteously solicited.

Respectfully submitted,

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